

Appl. No. : 09/853,080
Filed : May 9, 2001

A⁸
cont
light-chain peptide a3. As shown by western blotting, a3 is released from the A3 domain after thrombin treatment, preventing further binding of anti-(Arg¹⁶⁵²-Tyr¹⁶⁶⁴) Ig to activated FVIII. Similar results have been reported by Shima et al (1991), who described the FVIII sequence Asp¹⁶⁶³-Ser¹⁶⁶⁹ as a binding site of rabbit polyclonal antibodies neutralizing FVIII activity. Epitope Cys³²⁹-Asp³⁴⁸ overlapped the acidic Asp³⁴⁸-Lys³⁶² sequence (in a1) described as adjacent to the activated protein C (Arg³³⁶) and thrombin (Arg³⁷²) cleavage sites. It is the target of human hemophilic inhibitors. Anti-(Asp³⁴⁸-Lys³⁶²) antibodies may interfere with proteolysis or with the FX interaction site (Met³³⁷-Arg³⁷²) (Saenko et al., 1999 and Scandella et al., 2000).

See
A⁹
Please replace Table 1 and 2 on pages 38 to 41 with the attached Tables 1 and 2, on the pages numbered 38 to 41 (attached hereto immediately following the "marked up" version of Table 2).

IN THE CLAIMS

Please amend Claims 6 and 10 as follows:

A¹⁰
6. (Amended) An isolated or purified polypeptide comprising an epitope of factor VIII, wherein said epitope is selected from the group consisting of:

(a) the epitope arginine 1648 to tyrosine 1664 inclusive, defined by the following sequence:

SEQ ID NO: 1:

Arg Asp Ile Thr Arg Thr Thr Leu Gln Ser Asp Gln Glu Glu Ile Asp Tyr ,

(b) the epitope of (a) wherein one or more amino acids of the tetrapeptide Arg-Asp-Ile-Thr or one or two of the last amino acids of the peptide Asp-Tyr are deleted;

(c) the epitope aspartic acid 1681 to arginine 1696 inclusive, defined by the following sequence:

SEQ ID NO: 2:

Asp Glu Asp Glu Asn Gln Ser Pro Arg Ser Phe Gln Lys Lys Thr Arg ,

(d) the epitope of (c) wherein one or more amino acids of the epitope Asp-Glu-Asp-Glu are deleted;

(e) the epitope threonine 1739 to tyrosine 1748 inclusive, defined by the following sequence:

Appl. No. : **09/853,080**
Filed : **May 9, 2001**

SEQ ID NO: 3:

Thr Asp Gly Ser Phe Thr Gln Pro Leu Tyr;

(f) the epitope asparagine 1777 to phenylalanine 1785 inclusive, defined by the following sequence:

SEQ ID NO: 4:

Asn Gln Ala Ser Arg Pro Tyr Ser Phe ;

(g) the epitope of (f) wherein one or two amino acids of the terminal dipeptide Ser-Phe or the tetrapeptide Pro-Tyr-Ser-Phe are deleted;

(h) the epitope glutamic acid 1794 to tyrosine 1815 inclusive, defined by the following sequence:

SEQ ID NO: 5:

Glu Asp Gln Arg Gln Gly Ala Glu Pro Arg Lys Asn Phe Val Lys Pro

Asn Glu Thr Lys Thr Tyr ;

(i) the epitope of (h) wherein one or more amino acids from the first tripeptide Glu-Asp-Gln or the first nonapeptide Glu-Asp-Gln-Arg-Gln-Gly-Ala-Glu-Pro are deleted;

(j) the epitope methionine 1823 to aspartic acid 1831, defined by the following sequence:

SEQ ID NO: 6:

Met Ala Pro Thr Lys Asp Glu Phe Asp;

(k) the epitope glutamic acid 1885 to phenylalanine 1891 inclusive, defined by the following sequence:

SEQ ID NO: 7:

Glu Thr Lys Ser Trp Tyr Phe ;

(l) the epitope glutamic acid 1885 to alanine 1901 inclusive, defined by the following sequence:

SEQ ID NO: 8:

Glu Thr Lys Ser Trp Phe Thr Glu Asn Met Glu Arg Asn Cys Arg Ala ;

(m) the epitope of (l) wherein one or more amino acids from the heptapeptide Glu-Thr-Lys-Ser-Trp-Phe-Thr or from the tripeptide Cys-Arg-Ala are deleted;

(n) the epitope aspartic acid 1909 to arginine 1917 inclusive, defined by the following sequence:

SEQ ID NO: 9:

Appl. No. : 09/853,080
Filed : May 9, 2001

Asp Pro Thr Phe Lys Glu Asn Tyr Arg;

(o) the epitope comprised between serine 2018 and histidine 2031 inclusive, defined by the following sequence:

SEQ ID NO: 10:

Ser Asn Lys Cys Gln Thr Pro Leu Gly Met Ala Ser Gly His; and

(p) any of the preceding epitopes (a) to (o) wherein at least one amino acid has been deleted.

10. **(Amended)** An isolated or purified polypeptide comprising an epitope of factor VIII, wherein said epitope is selected from the group consisting of:

(a) the epitope aspartic acid 403 to lysine 425 inclusive, defined by the following sequence:

SEQ ID NO: 15:

Asp Asp Arg Ser Tyr Lys Ser Gln Tyr Leu Asn Asn Gly Pro Gln Arg

Ile Gly Arg Lys Tyr Lys Lys;

(b) the epitope of (a) wherein one or more amino acids of the tetrapeptide Asp-Asp-Arg-Ser are deleted;

(c) the epitope valine 517 to arginine 527 inclusive, defined by the following sequence:

SEQ ID NO: 16:

Val Glu Asp Gly Pro Thr Lys Ser Asp Pro Arg;

(d) the epitope of (c) wherein one or the two amino acids of the dipeptide Pro-Arg are deleted;

(e) the epitope tyrosine 555 to glutamine 565 inclusive defined by the following sequence:

SEQ ID NO: 17:

Tyr Lys Glu Ser Val Asp Gly Arg Gly Asn Gln;

(f) the epitope histidine 693 to glycine 701 inclusive, defined by the following sequence:

SEQ ID NO: 18

His Asn Ser Asp Phe Arg Asn Arg Gly;

(g) the epitope serine 710 to aspartic acid 725 inclusive, defined by the following sequence: